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FORMULATION AND EVALUATION OF SUSTAINED RELEASE MATRIX TABLET OF A MODEL DRUG

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ABSTRACT

Developing oral sustain release matrix tablet with constant release rate has always been a challenges to the pharmaceutical technology so that selecting appropriate polymers have become product of choice and important ingredient for formulating sustain release formulation. An appropriately designated control release drug delivery system is the major advance towards solving problem concerning targeting of drug to the specific organ or a tissue and controlling the rate of the drug deliver to the targeted site. This research article focuses on the progress made in design on sustained release dosage form implying various types of matrises as careers for the active ingredient.

KEYWORDS: Sustained release, control release, matrix and polymers.

1. INTRODUCTION

The basic rationale for controlled drug delivery is to alter the pharmacokinetics and pharmacodynamics of pharmacologically active moieties by using novel drug delivery system or by modifying the molecular structure and/or physiological parameters inherent in a selected route of administration.

1. Sustained Release Drug Delivery System

During the last two decades there has been remarkable increase in interest in sustained release drug delivery system. This has been due to various factor viz. the prohibitive cost of developing new drug entities, expiration of existing international patents, discovery of new polymeric materials suitable for prolonging the drug release, and the improvement in

therapeutic efficiency and safety achieved by these delivery systems. Now-a-days the technology of sustained release is also being applied to veterinary products.[1]

1) Controlled Release

These systems include any drug delivery system that achieves slow release of drug over an extended period of time.

2) Extended Release

Pharmaceutical dosage forms that release the drug slower than normal manner at predetermined rate & necessarily reduce the dosage frequency by two folds.

Controlled drug delivery systems have been developed which are capable of controlling the rate of drug delivery, sustaining the duration of therapeutic activity and/or targeting the delivery of drug to tissue.[2]

Optimal design of controlled release systems necessitates a thorough understanding of the pharmacokinetics and pharmacodynamics of the drug. The primary objectives of controlled drug delivery are to ensure safety and to improve efficacy of drugs as well as patient compliance. This is achieved by better control of plasma drug levels and less frequent dosing. The dose and dosing interval can be modified in case of conventional dosage forms. However, therapeutic window of plasma concentration below which no therapeutic effect is exhibited and above which undesirable effects are manifested. Therapeutic index is the prime parameter for development of a controlled delivery system of a particular drug candidate.[4,8]

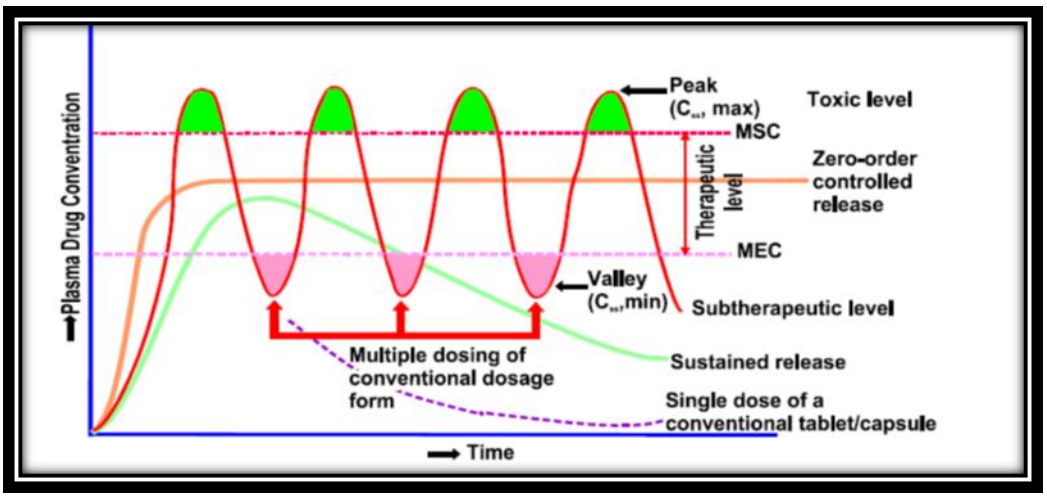

Figure 1: A hypothetical plasma concentration-time profile from conventional multiple dosing and single doses of sustained and controlled delivery formulations.

2. Sustained Release Matrix Systems

In a matrix system the drug is dispersed as solid particles within a porous matrix formed of a hydrophobic polymer (such as wax, polyethylene, polypropylene, and ethylcellulose) or hydrophilic polymer (such as hydroxipropylcellulose, hydroxipropylmethylcellulose, methylcellulose, sodiumcarboxymethylcellulose, alginates and scleroglucan). In this sense, the term "matrix" indicates the three dimensional network containing the drug and other substances such as solvents and excipients required for the specific preparation.[21]

Matrix drug delivery systems release the drug in continuous manner. These release the drug by both dissolution controlled as well as diffusion controlled mechanisms. Initially, drug particles located at the surface of the release unit will be dissolved and the drug released rapidly. In this system the drug reservoir is prepared by homogeneously dispersing drug particles in a rate controlling polymer matrix fabricated from either a lipophilic or a hydrophilic polymer.[22]

The drug is dispersed in the polymer matrix either by (1) blending a therapeutic dose of finely ground drug particles with a liquid polymer or a highly viscous base polymer, followed by cross-linking of the polymer chain,[23] (2) mixing drug and polymer at an elevated temperature. It can also be fabricated by dissolving the drug and the polymer in a common solvent, followed by solvent evaporation at an elevated temperature and/or under a vacuum.[24]

2.1 Advantages of Matrix Systems[3,25,27]

- Improvement of the ability to provide special effects.
- Easy to manufacture
- Versatile, effective and low cost
- Can be made to release high molecular weight compounds
- The sustained release formulations may maintain therapeutic concentrations over prolonged periods.
- The use of sustain release formulations avoids the high blood concentration.
- Sustain release formulations have the potential to improve the patient compliance.
- Reduce the toxicity by slowing drug absorption.
- Increase the stability by protecting the drug from hydrolysis or other derivative changes in gastrointestinal tract.

2.2 Disadvantages of Matrix Systems[25,27]

- Achievement of zero order release is difficult.
- The remaining matrix must be removed after the drug has been released.
- The drug release rates vary with the square root of time.
- Not all drugs can be blended with a given polymeric matrix.

2. MATERIALS AND METHOD

Material

Procurements of drugs and excipients

The drugs and excipients used for various experiments are enlisted as follows:

Table 1: List of drugs and excipients along with suppliers.

Sr. No.	Materials	Supplied/ Gifted by
1	Diltiazem HCl	Themis Pharmaceuticals Limited, Mumbai.
2	Stearic acid	Wockhardt research centre, Aurangabad
3	Stearyl alcohol	Wockhardt research centre, Aurangabad
4	Lactose monohydrate	Merck Chemicals, Mumbai.
5	Aerosil	S. D. Fine chemicals, Mumbai.

All chemicals and regents used were of analytical regent (AR) grade.

Method

Melt granulation Technique

Important steps involved in the wet granulation

I. Wax is melted in porcelain dish on a water bath maintained at constant temperature.

II. The Drug was gradually added to the molten wax with continuous stirring.

III. The molten mixture was allowed to cool and solidified at room temperature.

IV. The solidified mass was pulverized in mortar and sieved through a screen.

V. The granules passed through sieve were mixed with Glidant and compressed into a tablet with 10 mm deep concave punch using single punch tablet machine.

3. RESULTS AND DISCUSSION

A successful attempts was made to formulate sustained release tablets of Diltiazem HCL using Stearic acid and Stearyl alcohol. In the present, work six formulations were prepared whose composition is shown in Table. Effect of concentration and meltable binders in formulation development was assessed. Effect of type of meltable binder and effect of release enhancers such as lactose was studied. The formulated tablets were characterized for various physicochemical parameters.

FT-IR spectrum of drug

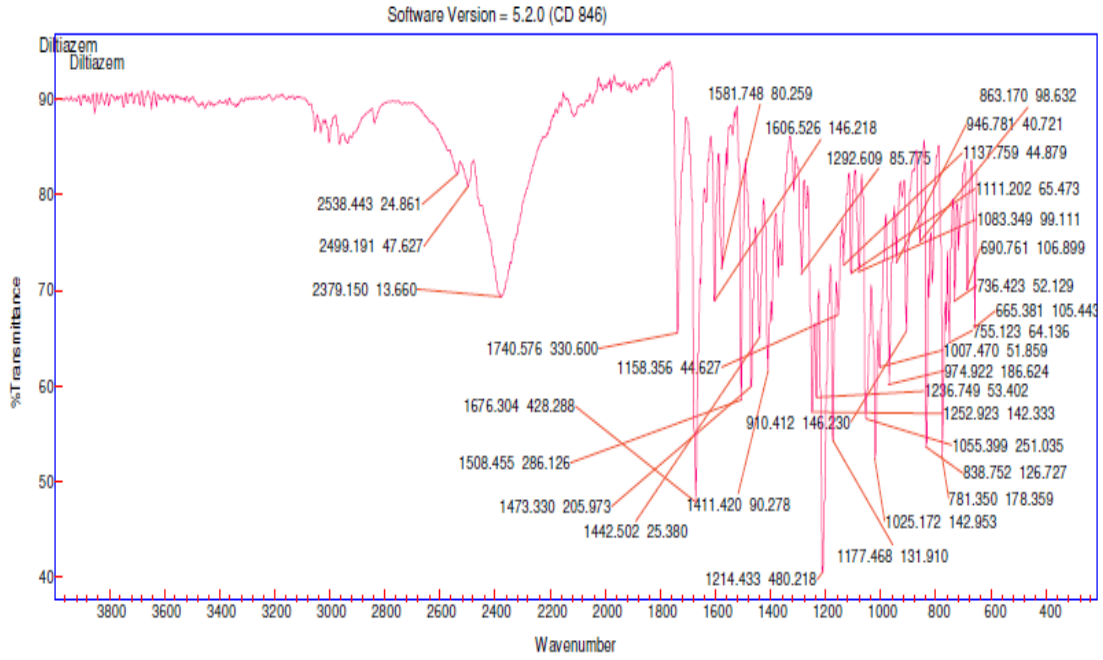

Figure 11: IR Spectra of Diltiazem HCl.

The IR spectrum of granules of formulation F1 and F4 prepared by melt granulation were studied. Spectrum of prepared granules were compared with that of pure drug IR spectra and were found to show no significant change in the appearance of characteristic peaks of pure drug spectra. This indicate that the drug is compatible with the meltable binders.

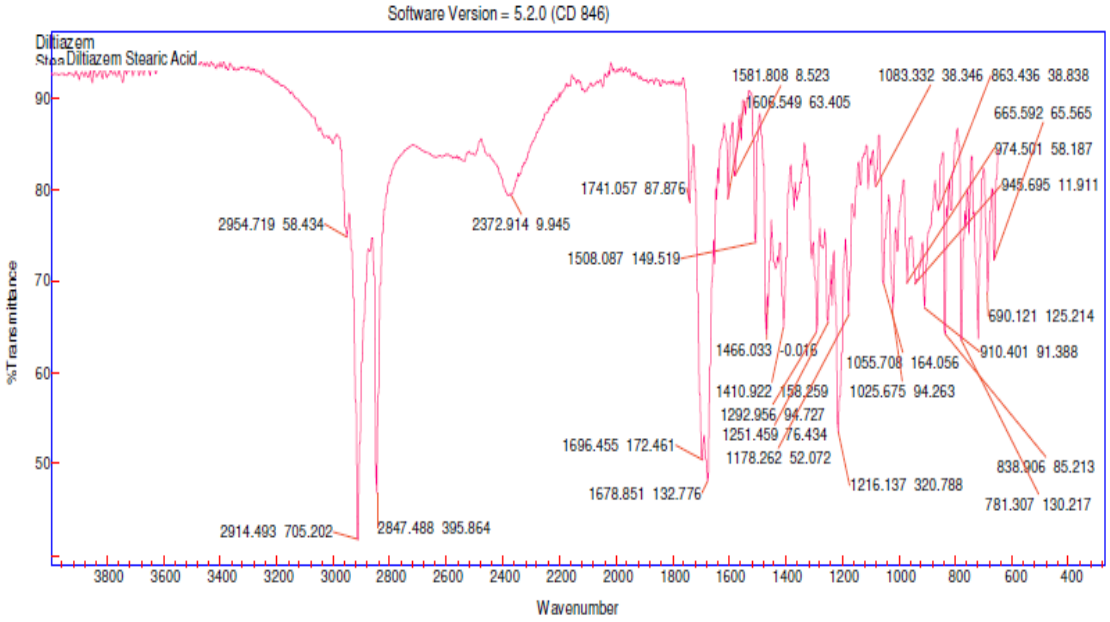

Figure 1: IR Spectra of Diltiazem HCl with Stearic acid.

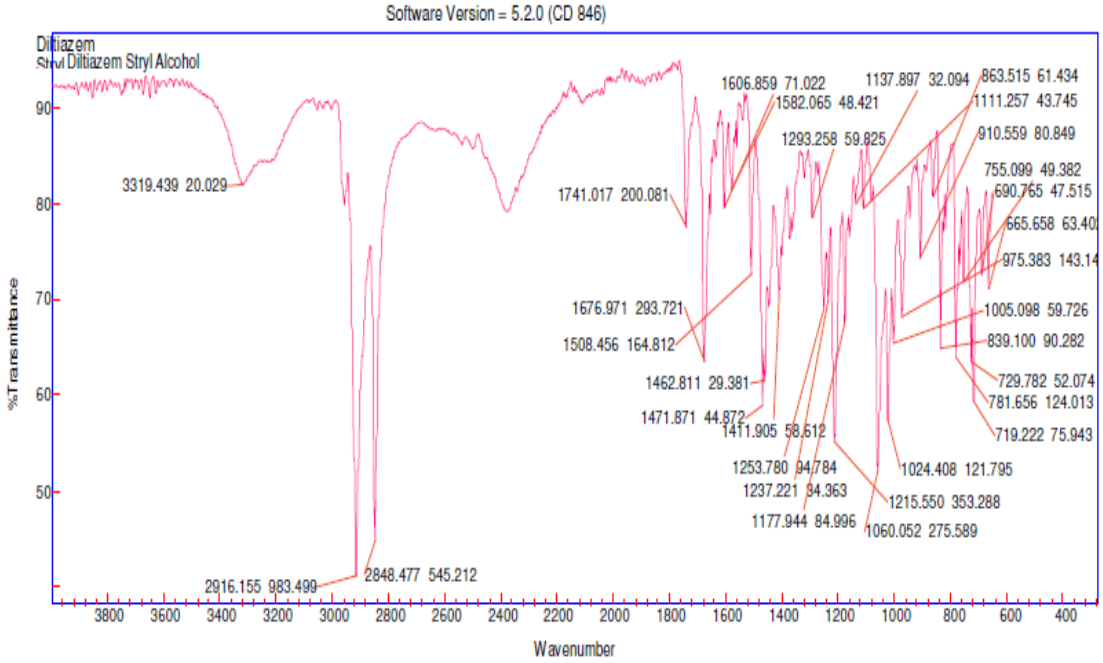

Figure 11: IR Spectra of Diltiazem HCl with Stearyl alcohol.

A. Evaluation of granules

All the formulation granules were evaluated for pre-compression parameters such as Angle of the repose, Loose Bulk Density, Tapped Bulk Density, Carr's Index and Hausner's Ratio and results obtained are shown in the table below.

Table 22: Evaluation of lubricated granules.

Formulation code	Bulk density (g/ml)	Tapped density (g/ml)	Angle of repose	Carr's index (%)	Hauser ratio
F1	0.443	0.508	29.05^0	12.69	1.145
F2	0.488	0.522	28.39^0	7.89	1.069
F3	0.466	0.528	27.66^0	11.76	1.133
F4	0.469	0.506	28.99^0	8.41	1.077
F5	0.455	0.495	28.50^0	8.68	1.089
F6	0.434	0.498	26.57^0	11.35	1.148

B. Evaluation of tablets

Formulation code	Thickness (mm)	Hardness (kg/cm^3)	Friability (%)	Weight Variation(mg)	Drug Content(%)
F1	5.39	4.43	0.41	397.1	99.07
F2	5.30	5.83	0.35	394.7	97.56
F3	5.27	6.15	0.25	398.2	98.11
F4	5.29	5.15	0.34	399.3	94.89
F5	5.24	5.75	0.26	401.8	98.66
F6	5.27	6.91	0.22	400.6	99.33

C. Release kinetics

Table 27: Kinetics of Diltiazem HCl matrix tablets.

Formulation Code	Zero Order (R^2)	First order (R^2)	Matrix Model (R^2)	Korsemeyer-peppas Model (R^2)	Hixson Crowell Model (R^2)
Marketed SR tablet	0.9276	0.9734	0.9481	0.9862	0.9664
F1	0.9217	0.9835	0.9867	0.9767	0.9690
F2	0.9685	0.9993	0.9894	0.9638	0.9842
F3	0.9257	0.9372	0.9688	0.9879	0.9865
F4	0.9653	0.9428	0.9842	0.9462	0.9994
F5	0.9565	0.9851	0.9467	0.9904	0.9639
F6	0.9629	0.9124	0.9871	0.9796	0.9278

Table 28: Model fitting for sustained release tablet of Diltiazem HCL.

Formulation code	N	k	r^2	Best fit Model
Marketed	0.8037	12.4519	0.9862	Peppas
F1	0.8361	12.5117	0.9867	Matrix
F2	0.7859	10.8169	0.9894	First order
F3	0.8277	13.6834	0.9879	Peppas
F4	0.7945	11.0989	0.9994	Hixson-Crowell
F5	0.8446	11.6545	0.9904	Peppas
F6	0.8285	13.5947	0.9871	Matrix

4. SUMMARY AND CONCLUSION

Sustained release drug delivery systems are designed to achieve a prolonged therapeutic effect by continuously releasing the medicament over an extended period of time.

Diltiazem HCL is a calcium channel-bloking agent having half-life of 3-4.5 hrs with the usual dose of 30-90 mg thrice daily. Because of high frequency of administration and short biological half-life, Diltiazem HCl was considered as a model drug for designing sustained release formulation. Also it has melting point of 214-218°C hence can be used for melt granulation technique. It is a drug of choice for stable and unstable angina pectoris, myocardial infarction, coronary artery spasm, hypertension and cardiac arrhythmias.

Melt granulation offers several advantages compared to conventional wet and dry granulation since the liquid addition and subsequent drying step are omitted. The process is less consuming in terms of time and energy compared to other methods. These fatty excipients have melting point in the range 45° to 80°C. By selecting lipophilic binders, melt granulation can be used for producing sustained release granules, pellets or matrix tablets.

In *in-vitro* dissolution studies different parameters like effect of concentration of lipophilic binders, effect of type of lipophilic binders, effect of release enhancers like lactose were studied. *In-vitro* release profile of all formulations was compared with marketed preparation Dilgard-90 SR.

From the results of the above mentioned study, it can be concluded that,

1. Lilipophilic binders (Stearic acid and Stearyl alcohol) are appropriate waxy materials that can be utilized as matrix forming agent to sustaine the release of Diltiazem HCL.
2. Drug release is inversely proportion to the level of rate retarding polymers present in matrix system i.e extent of drug release decrease with increase in wax content of the matrix.

F6 > F3

3. In-vitro drug release profile of formulation F2 resembles with that of marketed formulation hence considered as satisfactory formulation.
4. Stearic acid was found to be a good retardant science it forms thin coating on surface of drug particle. The slow release of drug could be due to the formation of uniform coating on individual drug particles by hydrophobic polymer during melt granulation. The results of dissolution studies indicates that the drug release retardation from lipophilic binders was in the following order:

Stearic Acid >Stearyl Alcohol

5. Drug release from matrix is primarily controlled by diffusion process. Higher the amount of hydrophobic polymer tends to show diffusion controlled release of drug.
6. The release kinetics model for matrices prepared by melt granulation showed the correction factor (R^2) for the best statistical lines revealed that first order model was better applicable to release data.
7. Drug release increases with increase in concentration of release enhancers such as lactose. It was due to rapid solubility of lactose and tendency to form pores in the matrix which allow the dissolution medium to penetrate the matrix and dissolve the drug.
8. Optimized formulation F2 was subjected to accelerated stability study. The data obtained from stability studies indicate that there is no much change in the release profile of tablets. Hence prepared tablets of F2 formulation is stable.

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